# Combien faut-il inclure de patients ?

## CALCUL DU NOMBRE DE SUJETS NÉCESSAIRES (NSN) POUR UN ESSAI DE SUPERIORITE

**Essai de démonstration de l'efficacité d'un nouveau traitement en comparaison à un placebo ou à un traitement de référence**


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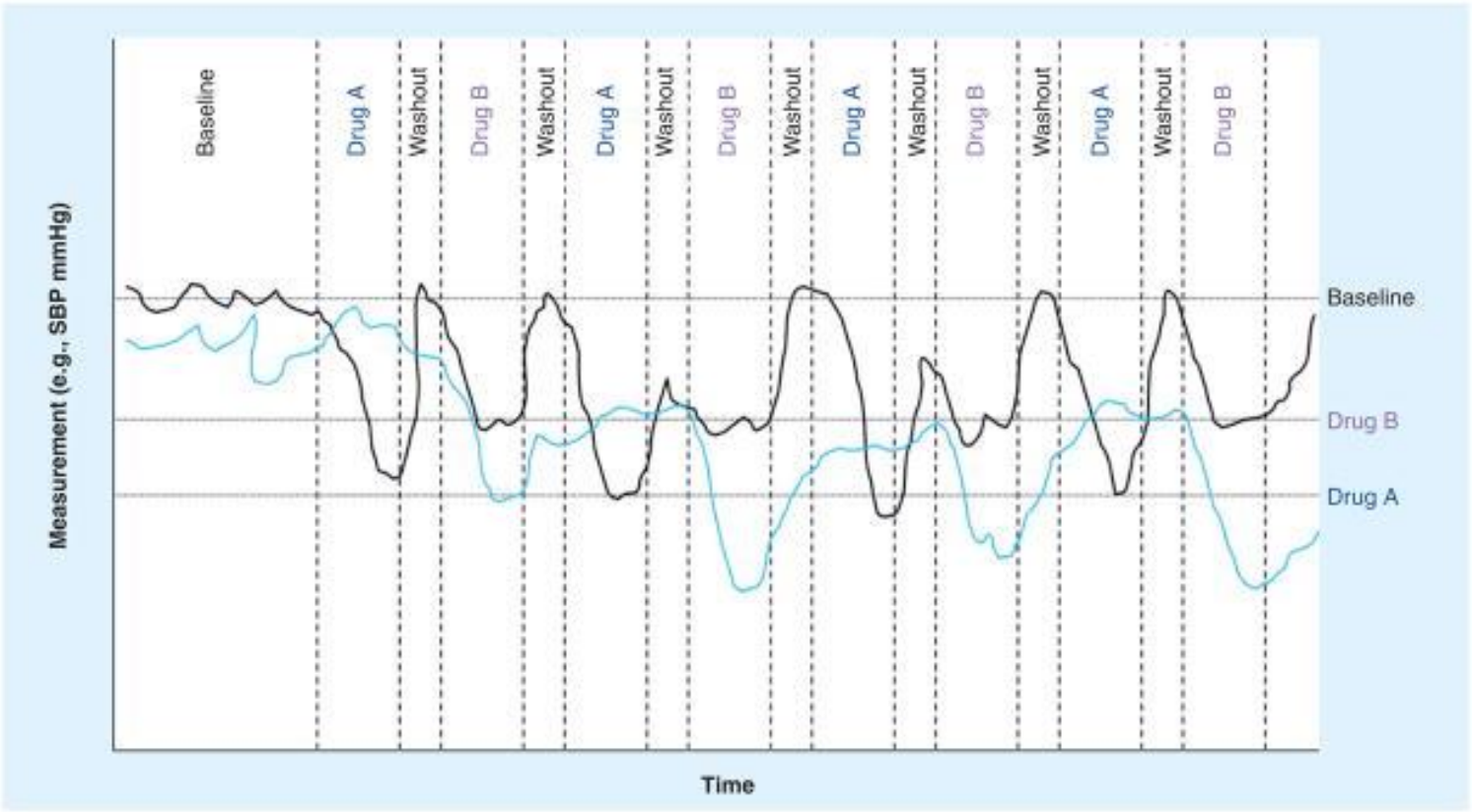
# BEAUCOUP

# n-of-1 clinical trial : does not apply to all situations




Hypothetical outcomes associated with two individual n-of-1 trials investigating the efficacy of two different antihypertensive medications

Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ.
The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Per Med. 2011 Mar;8(2):161-173.

# Calcul à partir d'hypothèses sur le critère d'évaluation

Mécanisme physiopathologique

↓

Molécule intéressante

↓

Question

↓

Protocole d'étude

↓

**CRITÈRE PRINCIPAL D'ÉVALUATION**

↓

**CALCUL DU NOMBRE DE SUJETS NÉCESSAIRE**

↓

Réalisation essai

↓

**Analyse statistique sur le critère principal**

↓

**Conclusion essai**

# Tout le problème…

| | Groupe A | Groupe B | Différence |
|---|---|---|---|
| Critère | 40% | 60% | Δ = 20% |
| si | n = 200 | n = 200 | p = 0,0001 |
| si | n = 20 | n = 20 | p = 0,2 NS |

**Les conclusions sont opposées…**

# Pivoxil amdinocilline versus triméthoprime – sulfaméthoxazole en traitement oral ambulatoire dans les prostatites aiguës

RÉSUMÉ : Un essai thérapeutique oral ambulatoire de pivoxil amdinocilline (Selexid) versus triméthoprime-sulfaméthoxazole (Bactrim) a été effectué par 8 praticiens dans 47 cas de prostatites aiguës. A un mois, la guérison est constatée pour 22 des 24 patients Selexid et 20 des 22 patients Bactrim ; l'amélioration est constatée pour 2 des 24 patients Selexid et 2 des 22 patients Bactrim. A un an, la guérison est constatée pour 22 des 24 patients Selexid et 19 des 22 patients Bactrim : 3 récidives sont rapportées : deux patients Selexid, un patient Bactrim ; un patient Selexid et deux patients Bactrim ne sont pas revus à un an. Cet essai comparatif, en double aveugle avec double placebo, de l'efficacité et de la tolérance du Selexid et de l'antibiotique de référence, Bactrim, prescrits pendant 21 jours fait apparaître les difficultés de recrutement précoce des patients à la phase initiale de la prostatite aiguë ; il ne met pas en évidence de différence statistiquement significative entre les deux traitements.

# Calcul du nombre de sujets nécessaires (NSN)

## à partir du critère principal : 5 variables

**1. Risque α (1ère espèce) : fixé généralement à 5%**

- risque de trouver à tort une différence significative qui n'existe pas

**2. Risque ß (2ème espèce) : fixé entre 5%-10%-20%**

- risque de "passer à coté" d'une différence significative qui existe réellement : manque de puissance (puissance = 1 - ß)

**3. Différence escomptée Δ**

- Bénéfice thérapeutique attendu, différence cliniquement intéressante

**4. Variance σ2**

- Dispersion des valeurs du critère de jugement (si variable quantitative)

**5. Formulation unilatérale ou bilatérale**

# Δ= DIFFÉRENCE ESCOMPTÉE

- entre 2 pourcentages : P - P’ = Δ
- entre 2 moyennes : μ - μ’ = Δ

**Si Δ escomptée est importante :**

➔ l'essai sera simple

➔ avec un nombre limité de patients

➔ mais cet essai risque de ne pas montrer de différence significative, si la différence observée (réelle) est plus faible que celle escomptée prise pour le calcul du NSN

« Excès d'optimisme »

➔ **Un effectif réduit ne permet de déceler qu’une grande différence**

**exemple : < 200 patients correspond une différence > 20%**

# Δ= DIFFÉRENCE ESCOMPTÉE

- entre 2 pourcentages : P - P’ = Δ
- entre 2 moyennes : μ - μ’ = Δ

**Si Δ escomptée est faible :**

➔ l'essai sera long

➔ avec un grand nombre de patients

➔ et si l'on met en évidence une différence statistiquement significative entre les 2 groupes, quelle est la pertinence de ce bénéfice thérapeutique au vu de cette petite différence ?

# La pertinence de la différence escomptée dépend du critère d'évaluation

- La pertinence clinique d'une différence n'est pas la même suivant le critère d'évaluation

- **<u>Différence de 2%</u>**
  - Sur la valeur de pression artérielle
    - 150 vs 147 mm Hg de pression systolique

      → Pas pertinent
  - **Sur la mortalité cardiovasculaire**
    - **4% vs 2%**

      → Très pertinent

# Calcul approximatif du nombre de sujets nécessaires (essai de supériorité) Variable qualitative (%)

| Hypothèse nouveau médicament | Hypothèse bras de comparaison | Différence absolue attendue | Nombre total de sujets à inclure |
|---|---|---|---|
| 70%* | 40%* | **30%** | **100** |
| 65%* | 40%* | **25%** | **150** |
| 60%* | 40%* | **20%** | **200** |
| 55%* | 40%* | **15%** | **400** |
| 50%* | 40%* | **10%** | **800** |
| 2%** | 4%** | **2%** | **2 500** |
| 0,5%** | 1%** | **0,5%** | **10 000** |

* Par exemple : taux de répondeurs (douleur, symptôme, HbA1c < 6%, …)

** Par exemple : taux de mortalité, de complications digestives majeures…

# Essai randomisé en double-aveugle comparant Aérosol de salbutamol avec ou sans bromure d'ipratropium dans l'obstruction des aiguë des voies aériennes (Lancet 1989)

| Le tirage au sort était effectué selon l'année de naissance (paire, impaire) | **Salbutamol** | **Salbutamol + ipratropium** |
|---|---|---|
| Total échantillon | **44** | **59** |
| Sous-groupe : Patients asthmatiques | **23** | **33** |
| Sous-groupe : Asthmatiques sévères (Débit expiratoire de pointe – DEP < 140 l/mn) | **12** | **33** |
| Sous-groupe : BPCO (Bronchite chronique obstructive) | **21** | **26** |

**→ Sans stratification, la constitution « post-hoc » de sous-groupes aboutit le plus souvent à des groupes non comparables**

# Octreotide infusion or emergency sclerotherapy for variceal haemorrhage (Lancet 1993; 342)

*Statistical methods*

Based on an expected efficacy of 85% in the octreotide group and 90% in the sclerotherapy group (derived from our experience with sodium tetradecyl sulphate injection), with a two-tailed test to achieve a statistical power of 80% and a 5% α error, we estimated that at least 900 patients in each group were needed. It is unlikely, therefore, that a clinical trial of a reasonable size can reach such a statistical power. We arbitrarily set a target of 100 patients and accepted a chance of type II error.

Data are given as mean (SE) or percentages with 95% confidence intervals (CI). Student's *t* test was used for continuous variables and the two-tailed Fisher's exact test for categorical variables. The non-parametric Mann-Whitney U test was used for comparison of blood transfusion and duration of hospital stay. For mortality assessment, the Kaplan-Meier method was used to construct life-tables, and the non-parametric log-rank test was used to assess differences between groups. Cox's proportional hazards model was used to evaluate relative risk for independent prognostic factors.

# Octreotide infusion or emergency sclerotherapy for variceal haemorrhage (Lancet 1993; 342)

**Abstract. To compare octreotide with injection sclerotherapy in the treatment of acute variceal haemorrhage, patients admitted with gastrointestinal bleeding and oesophageal varices confirmed by endoscopy were randomised to receive either emergency sclerotherapy with 3% sodium tetradecyl sulphate or octreotide (50 µg intravenous bolus plus 50 µg per h intravenous infusion for 48h). At the end of the study period (48h), the octreotide group also had sclerotherapy to obliterate the varices. 100 patients were recruited. Demographic features including the aetiology of portal hypertension and the Child- Pugh's grading of the two groups were similar. Bleeding was initially controlled in 90% of patients by emergency sclerotherapy and in 84% by octreotide infusion (95% confidence interval 0-19.5, P=0.55). There were no significant differences between the two groups in early rebleeding (16% vs 14%), blood transfusion (3 units vs 3.5), hospital stay (5 days vs 6 days), or hospital mortality (27% vs 20%). No notable side-effects were associated with octreotide. We conclude that octreotide infusion and emergency sclerotherapy are equally effective in controlling variceal haemorrhage.**

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**Ne pas démontrer de différence dans un essai de supériorité n'équivaut pas à équivalence**

**Altman D et al. Absence of evidence is not evidence of equivalence. BMJ 1995; 311: 485.**

# Taille de l'échantillon dans les cohortes observationnelles longitudinales

- Plusieurs centaines à milliers de patients suivis sur une période pouvant aller jusqu'à plusieurs années :
- Fonction de :
  - Incidence de l'évènement étudié
  - Délai d'apparition
  - Analyses multivariées

# Sample size for observational cohort example in psoriatic arthritis (PsA)

- To determine the incidence of malignancies in patients with PsA who are taking conventional and biologic therapies.
- **618 patients with PsA were included. 296 were taking anti-TNF and 322 were taking disease-modifying antirheumatic (DMARD).**
- **44 patients** (7.1%) had a diagnosis of malignancy.
  - 14 (4.7%; 0.52/100 patient-yrs) received anti-TNF therapy
  - 30 (9.3%; 1.03/100 patient-yrs) received DMARD (p = 0.019)
- After adjusting for major demographic and clinical characteristics, the difference between the 2 treatments was no longer significant, and the only predictor of malignancy occurrence was age (HR 1.04, 95% CI 1.009-1.073, p = 0.012).
- Biological therapies do not lead to any increased risk for cancer.

Costa L, et al. Incidence of Malignancies in a Cohort of Psoriatic Arthritis Patients Taking Traditional Disease Modifying Antirheumatic Drug and Tumor Necrosis Factor Inhibitor Therapy: An Observational Study. J Rheumatol. 2016 Sep 15. pii: jrheum.160542

# Sample size for observational cohort example in psoriasis

- Psoriasis induced by anti-tumor necrosis factor-α (TNF) therapy has been described as a paradoxical side effect.
- To determine the incidence, of psoriasis induced by anti-TNF therapy in a large nationwide cohort of inflammatory bowel disease patients.
- Anti-TNF-induced psoriasis was reported in **125 of 7415 patients treated with anti-TNFs (1.7%; 95% CI, 1.4-2)**.
  - The incidence rate of psoriasis is 0.5% (95% CI, 0.4-0.6) per patient-year.
  - In the multivariate analysis, the female sex (HR 1.9; 95% CI, 1.3-2.9) and being a smoker/former smoker (HR 2.1; 95% CI, 1.4-3.3) were associated with an increased risk of psoriasis.
  - …

Guerra I, Spanish GETECCU group (ENEIDA project). Incidence, Clinical Characteristics, and Management of Psoriasis Induced by Anti-TNF Therapy in Patients with Inflammatory Bowel Disease: A Nationwide Cohort Study. Inflamm Bowel Dis. 2016 Apr;22(4):894-901.

# Level of evidence
# Causality versus Association

Non randomized study (cohort / observational)

Conclusion = Association

Randomized controlled clinical trial

Conclusion = Causality

# Les études peuvent être classées selon un niveau de preuve

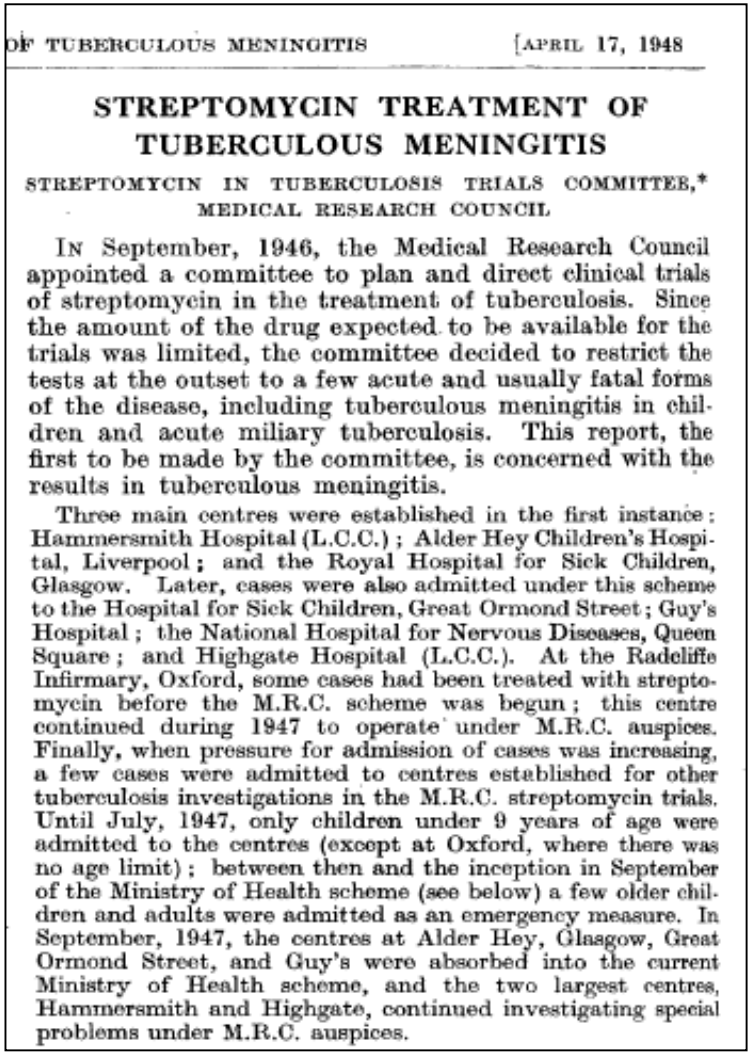
| Niveau de preuve scientifique | | Force des recommandations |
|---|---|---|
| I | •Grands essais comparatifs randomisés avec résultats indiscutables<br>•Méta-analyse | A |
| II | •Petits essais comparatifs randomisés et/ou résultats incertains | B |
| III | •Essais comparatifs non randomisés, mais avec groupes de sujets témoins contemporains<br>•Suivi de cohorte | C |
| IV | •Essais comparatifs non randomisés avec groupes de sujets témoins historiques<br>•Etudes cas-témoins | |
| V | •Pas de groupe de sujets témoins, série de patients | |

# Do we still need rigorous and complicated RCT today ?

## YES

Even more since nowadays the expected therapeutic benefits of a new treatment is more and more tiny compared to effective and available treatment in many diseases (and such more difficult to show)

**Exception : Efficacy of streptomycin in tuberculosis meningitis is solely based on cohorts, but because disease was 100% lethal (1948)**



OF TUBERCULOUS MENINGITIS [APRIL 17, 1948

### STREPTOMYCIN TREATMENT OF TUBERCULOUS MENINGITIS

STREPTOMYCIN IN TUBERCULOSIS TRIALS COMMITTEE,* MEDICAL RESEARCH COUNCIL

In September, 1946, the Medical Research Council appointed a committee to plan and direct clinical trials of streptomycin in the treatment of tuberculosis. Since the amount of the drug expected to be available for the trials was limited, the committee decided to restrict the tests at the outset to a few acute and usually fatal forms of the disease, including tuberculous meningitis in children and acute miliary tuberculosis. This report, the first to be made by the committee, is concerned with the results in tuberculous meningitis.

Three main centres were established in the first instance: Hammersmith Hospital (L.C.C.); Alder Hey Children's Hospital, Liverpool; and the Royal Hospital for Sick Children, Glasgow. Later, cases were also admitted under this scheme to the Hospital for Sick Children, Great Ormond Street; Guy's Hospital; the National Hospital for Nervous Diseases, Queen Square; and Highgate Hospital (L.C.C.). At the Radcliffe Infirmary, Oxford, some cases had been treated with streptomycin before the M.R.C. scheme was begun; this centre continued during 1947 to operate under M.R.C. auspices. Finally, when pressure for admission of cases was increasing, a few cases were admitted to centres established for other tuberculosis investigations in the M.R.C. streptomycin trials. Until July, 1947, only children under 9 years of age were admitted to the centres (except at Oxford, where there was no age limit); between then and the inception in September of the Ministry of Health scheme (see below) a few older children and adults were admitted as an emergency measure. In September, 1947, the centres at Alder Hey, Glasgow, Great Ormond Street, and Guy's were absorbed into the current Ministry of Health scheme, and the two largest centres, Hammersmith and Highgate, continued investigating special problems under M.R.C. auspices.